

Stereochemistry of 3,3'-Bithienyls

II.* An Intramolecular Cannizzaro Reaction. On the Synthesis, Resolution, and Lactonization of *o*-Carboxy-*o*'-hydroxymethyl-3,3'-bithienyls

ERIK WIKLUND and ROLF HAKANSSON

Chemical Center, Division of Organic Chemistry, University of Lund, Box 740, S-220 07 Lund 7, Sweden

A recent paper by Wynberg and Sinnige¹ on the synthesis of dithienobenzoquinones from dialdehydes I and IV, R=H, by an intramolecular benzoin condensation prompts us to report an intramolecular Cannizzaro reaction on dialdehydes I and IV, R=Br or CH₃, yielding 2-carboxy-2'-hydroxymethyl-3,3'-bithienyls (II) and 4-carboxy-4'-hydroxymethyl-3,3'-bithienyls (V).

In a review of cyclization reactions of 2,2'-disubstituted biphenyls² only one previous intramolecular Cannizzaro reaction in a biaryl system is mentioned. By the action of potassium hydroxide on 2,2'-diformylbiphenyl, Kenner and Turner³ in 1911 obtained a hydroxy acid together with the corresponding lactone. Another example of an intramolecular Cannizzaro reaction is the formation of phthalide when *o*-phthalaldehyde is treated with strong alkaline solution.⁴

The dialdehydes in the scheme were prepared in the following way: 4,4'-Dibromo-2,2'-diformyl-3,3'-bithienyl (Ia), m.p. 167–168.5°, was obtained in 68% yield from 2,2'-4,4'-tetrabromo-3,3'-bithienyl⁵ by halogen-metal interconversion at –70° followed by reaction of the intermediate 2,2'-dilithium derivative with *N,N*-dimethylformamide (DMF). The aldehyde functions were easily protected by acetal formation. The bisdimethyl acetal, m.p. 140–141°, was obtained in 81% yield on dissolving Ia in a small volume of boiling acidified methanol and cooling the solution in a refrigerator. Renewed bromo-lithium exchange at –70° yielded a 4,4'-dilithium derivative which was reacted with dimethyl sulphate.⁶ Hydrolysis of the acetal gave 2,2'-diformyl-4,4'-dimethyl-3,3'-bithienyl (Ib), m.p. 134.5–135.5°, in 57% yield. Reacting 4,4'-dibromo-3,3'-bithienyl⁷ at –70° with alkyl lithium and then with DMF gave 4,4'-diformyl-3,3'-bithienyl, m.p. 169.5–170°, in 58% yield. This dialdehyde was brominated in 59% yield to 2,2'-dibromo-4,4'-diformyl-3,3'-bithienyl (IVa), m.p. 155–155.5°, analogous to the bromination of 3-formylthiophene in methylene chloride in the presence of aluminium chloride.⁸ The reaction of 4,4'-dibromo-2,2'-dilithium-3,3'-bithienyl, obtained as above from 2,2',4,4'-tetrabromo-3,3'-bithienyl, with dimethyl sulphate gave a 70% yield of 4,4'-dibromo-2,2'-dimethyl-3,3'-bithienyl, m.p. 76–78°. Bromo-lithium exchange at –70° and subsequent reaction of the intermediate 4,4'-dilithium derivative with DMF gave 4,4'-diformyl-2,2'-dimethyl-3,3'-bithienyl (IVb), m.p. 108–110°, in 62% yield.

* For part I, see Ref. 5.

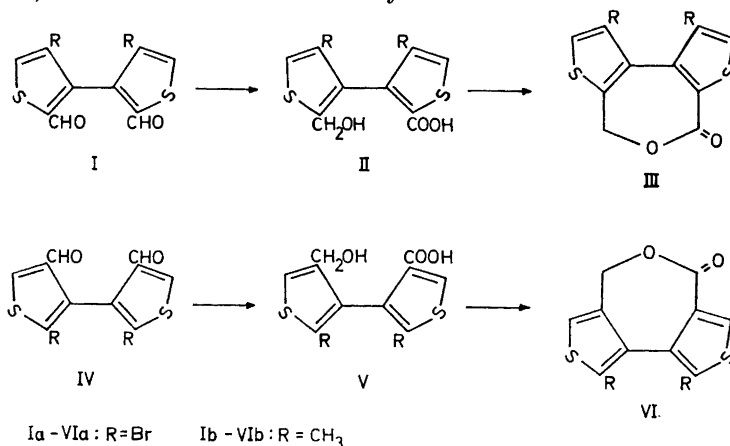


Table 1. Yields, melting points, and optical data^a for some hydroxy acids, diacids, lactones, and methyl esters in the 3,3'-bithienyl series.

Compound	Yield %	Racemic M.p. °C	Optically active M.p. °C	$[\alpha]_D^{25}$
IIa Acid	88	161 - 162	155.5 - 157.5	9.8
Ester	77	91.5 - 92	106.5 - 107	30
IIIa	77	215 - 217	—	48
Va Acid	86	153 - 153.5	152.5 - 153.5	65
Ester	78	81.5 - 83.5	88 - 88.5	42
VIa	82	192 - 192.5	—	—
IIb	86	—	—	—
IIIb	60	128.5 - 130	—	—
Vb	82	141.5 - 142.5	—	—
VIb	64	154.5 - 155.5	—	—
VII Acid	51	302d	255 - 258 ^b	44
Ester	85	161 - 162	138.5 - 139	54
VIII Acid	52	265d	135 - 140 ^b	85
Ester	82	100 - 101	84 - 86	76

^a The optical activities were measured on ethanolic solutions.

^b At higher temperature the acid crystallized and remelted at the same temperature as the racemic form.

The intramolecular Cannizzaro reaction was carried out with the dialdehydes in methanolic potassium hydroxide solution at 70–80° for 1 h. After cooling, diluting with water and acidification the hydroxy acids slowly crystallized, except for IIb which first gave an oil. Data are given in Table 1.

4,4'-Dibromo-2-carboxy-2'-hydroxymethyl-3,3'-bithienyl (IIa) and 2,2'-dibromo-4-carboxy-4'-hydroxymethyl-3,3'-bithienyl (Va) have been resolved into optical antipodes by fractional crystallization of the corresponding brucine salts from ethanol. The maximum activities obtained in ethanol are given in Table 1. IIa was optically pure after one crystallization. 2-Carboxy-2'-hydroxymethyl-4,4'-dimethyl-3,3'-bithienyl (IIb) and 4-carboxy-4'-hydroxymethyl-2,2'-dimethyl-3,3'-bithienyl (Vb) have not yet been resolved.

Oxidation of the racemic hydroxy acids IIa and Va in boiling alkaline potassium permanganate solution for 5 min gave 4,4'-dibromo-2,2'-dicarboxy-3,3'-bithienyl⁵ (VII) and 2,2'-dibromo-4,4'-dicarboxy-3,3'-bithienyl (VIII), respectively. The optically active hydroxy acids in the same way yielded the corresponding optically active diacids. (+)-IIa gave (+)-VIIa and (+)-Va gave (+)-VIIIa. Melting points and optical data are given in Table 1.

Methyl esters of some of the acids have been obtained with diazomethane (Table 1). The optically active ester in each case had the same mode of rotation as its acid.

All hydroxy acids in the scheme gave the corresponding ϵ -lactones, 4,4'-dibromo-2-carboxy-2'-hydroxymethyl-3,3'-bithienyl lactone (IIIa), 2-carboxy-2'-hydroxymethyl-4,4'-dimethyl-3,3'-bithienyl lactone (IIIb), 2,2'-dibromo-4-carboxy-4'-hydroxymethyl-3,3'-bithienyl lactone (VIa), and 4-carboxy-4'-hydroxymethyl-2,2'-dimethyl-3,3'-bithienyl lactone (VIb), by treatment in boiling toluene for one hour in the presence of *p*-toluenesulphonic acid as a catalyst. The optically active bromo compound IIa gave a partly racemic product, which was evident from the semicrystalline state of the optically active sample, the well-crystallized part of which showed no activity. That the optical activity of the lactone product did not originate from unreacted IIa was evident from the different mode of rotation [(+)-IIa \rightarrow (-)-IIIa] and from IR, and CD spectra. As present we do not know if it really is IIIa or a by-product which is optically active.

The optically active bromo compound Va yielded an apparently racemic lactone both if the reaction was carried out as above or at room temperature with *p*-

toluenesulphonyl chloride in pyridine for 10 min. Under the latter conditions optically active IIa gave a lactone with lower activity than if obtained from hot toluene. In PMR the magnetic nonequivalent methylene protons of lactones III and VI exhibited an AB pattern ($J=13-14$ cps) if dimethyl sulphoxide was used as solvent. Only one of the methylene protons in VIa and VIb showed in addition the characteristic long range coupling to the hydrogens at the 5,5'-positions ($J=0.5$ cps) observed in 4-methylthiophenes. The methylene resonances collapsed to a singlet at about 135° in lactone IIIa ($\Delta G_c^\ddagger=20.6$ kcal/mole) and at about 131° in lactone VIa ($\Delta G_c^\ddagger=20.4$ kcal/mole). Further investigations are in progress.

Detailed descriptions of the syntheses, resolutions and the various experiments will be published later.

Correct microanalyses were obtained for all new compounds except IIb. The crude hydroxy acid, however, gave a pure lactone. All melting points given above are uncorrected.

In a conformationally rigid lactone such as III or VI, both the biaryl dihedral angle as well as the twist of the ester group in relation to the ring planes are fixed. A spectropolarimetric study of the optically active lactones would give information about the significance of a twisted aryl ester as an inherently dissymmetric chromophore.⁹

Acknowledgements. The authors want to thank Professor Salo Gronowitz for his kind interest in this work and for all facilities put at their disposal. Grants from *The Faculty of Science of the University of Lund* and *The Royal Physiographic Society in Lund* are gratefully acknowledged.

1. Wynberg, H. and Sinnige, H. J. M. *Rec. Trav. Chim.* **88** (1969) 1244.
2. Buntrock, R. E. and Taylor, E. C. *Chem. Rev.* **68** (1968) 209.
3. Kenner, J. and Turner, E. G. *J. Chem. Soc.* **99** (1911) 2101.
4. Thiele, J. and Günther, O. *Ann.* **347** (1907) 107.
5. Håkansson, R. and Wiklund, E. *Arkiv Kemi* **31** (1969) 101.
6. Ramanathan, V. and Levine, R. *J. Org. Chem.* **27** (1962) 1667.
7. Gronowitz, S. *Acta Chem. Scand.* **15** (1961) 1393.

Acta Chem. Scand. **24** (1970) No. 1

8. Fournari, P., Guillard, R. and Person, M. *Bull. Soc. Chim. France* **1967** 4115.

9. Mislow, K., Glass, M. A. W., Hopps, H. B., Simon, E. and Wahl, Jr., G. H. *J. Am. Chem. Soc.* **86** (1964) 1710.

Received December 5, 1969.

A New Method for the Preparation of α -Pyrone from β -Diketones

A. K. SØRENSEN and N. A. KLITGAARD

Danish Civil Defence Analytical-Chemical Laboratory, Universitetsparken 2, DK-2100 Copenhagen, Denmark

During attempts to prepare unsaturated pimelic acids from β -diketones (I) and ethoxycarbonylmethylenetriphenylphosphorane (II) by a Wittig-reaction, some 4,6-disubstituted α -pyrones (IV), of which IVc and IVd are new, have been isolated. When 2-benzoylcyclohexanone (V) is used as a starting material, the new 4,5,6-trisubstituted α -pyrone VIa is formed.

Although it is known that II reacts very slowly with monoketones, a few successful reactions having been reported,³⁻⁵ it appears that reactions between II and β -diketones have not been described previously. The syntheses with which this paper is concerned are performed by mixing I or V with II and then heating the mixture in a closed tube. Only β -diketones I in which R and R' are identical have been investigated. It is probable that the first step in the synthesis is a reaction between II and one of the keto groups of I to form III, in accordance with the Wittig-reaction. The enol form of III could then immediately form IV by ring closure. The reaction between II and V probably also follows this course.

IVa has been synthesized from benzoylphenylacetylene and ethyl *p*-toluoylacetate¹ by a Michael-addition, and IVb has been prepared from β -(4-methoxyphenyl)-glutaconic anhydride and anisole² by a Friedel-Crafts' reaction. The melting points of IVa and IVb prepared here were in good accordance with those given in the literature.^{1,2}